```
=> file .nash
=> s estrogen receptor and agonist and activator
L1          77 FILE MEDLINE
L2          89 FILE CAPLUS
L3          70 FILE SCISEARCH
L4          17 FILE LIFESCI
L5          39 FILE BIOSIS
L6          53 FILE EMBASE

TOTAL FOR ALL FILES
L7         345 ESTROGEN RECEPTOR AND AGONIST AND ACTIVATOR

=> s l7 and crystal?
TOTAL FOR ALL FILES
L14         25 L7 AND CRYSTAL?

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15          16 DUP REM L14 (9 DUPLICATES REMOVED)

=> d ibib abs 1-15

L15  ANSWER 1 OF 16     MEDLINE on STN                  DUPLICATE 1
ACCESSION NUMBER:   2004412357     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 15161930
TITLE:              Structural basis for the deactivation of the
                    estrogen-related receptor gamma by diethylstilbestrol or
                    4-hydroxytamoxifen and determinants of selectivity.
AUTHOR:             Greschik Holger; Flaig Ralf; Renaud Jean-Paul; Moras Dino
CORPORATE SOURCE:   Departement de Biologie et Genomique Structurales, Institut
                    de Genetique et de Biologie Moleculaire et Cellulaire, 1
                    rue Laurent Fries, B. P. 10142, 67404 Illkirch, France.
SOURCE:             Journal of biological chemistry, (2004 Aug 6) 279 (32)
                    33639-46.
                    Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
OTHER SOURCE:       PDB-1S9P; PDB-1S9Q; PDB-1TFC; PDB-1VJB
ENTRY MONTH:        200410
ENTRY DATE:         Entered STN: 20040820
                    Last Updated on STN: 20041026
                    Entered Medline: 20041025
AB   The estrogen-related receptor (ERR) gamma behaves as a constitutive
     activator of transcription. Although no natural ligand is known,
     ERRgamma is deactivated by the estrogen receptor (ER)
     agonist diethylstilbestrol and the selective ER modulator
     4-hydroxytamoxifen but does not significantly respond to estradiol or
     raloxifene. Here we report the crystal structures of the
     ERRgamma ligand binding domain (LBD) complexed with diethylstilbestrol or
     4-hydroxytamoxifen. Antagonist binding to ERRgamma results in a rotation
     of the side chain of Phe-435 that partially fills the cavity of the
     apoLBD. The new rotamer of Phe-435 displaces the "activation helix"
     (helix 12) from the agonist position observed in the absence of
     ligand. In contrast to the complexes of the ERalpha LBD with
     4-hydroxytamoxifen or raloxifene, helix 12 of antagonist-bound ERRgamma
     does not occupy the coactivator groove but appears to be completely
     dissociated from the LBD body. Comparison of the ligand-bound LBDs of
     ERRgamma and ERalpha reveals small but significant differences in the
     architecture of the ligand binding pockets that result in a slightly
     shifted binding position of diethylstilbestrol and a small rotation of
     4-hydroxytamoxifen in the cavity of ERRgamma relative to ERalpha. Our
     results provide detailed molecular insight into the conformational changes
     occurring upon binding of synthetic antagonists to the constitutive orphan
     receptor ERRgamma and reveal structural differences with ERs that explain
     why ERRgamma does not bind estradiol or raloxifene and will help to design
     new selective antagonists.

L15  ANSWER 2 OF 16  CAPLUS  COPYRIGHT 2004 ACS on STN
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ACCESSION NUMBER: 2003:537006 CAPLUS
DOCUMENT NUMBER: 139:240508
TITLE: Mutation of Leu-536 in human **estrogen receptor**-.alpha. alters the coupling between ligand binding, transcription activation, and receptor conformation
AUTHOR(S): Zhao, Changqing; Koide, Akiko; Abrams, Judith; Deighton-Collins, Sarah; Martinez, Angela; Schwartz, Janice A.; Koide, Shohei; Skafar, Debra F.
CORPORATE SOURCE: Department of Physiology, Wayne State University School of Medicine, Detroit, MI, 48201, USA
SOURCE: Journal of Biological Chemistry (2003), 278(29), 27278-27286
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **estrogen receptor** (ER), of which there are two forms, ER.alpha. and ER.beta., is a ligand-modulated transcription factor important in both normal biol. and as a target for agents to prevent and treat breast cancer. **Crystallog**. studies of the ER.alpha. ligand-binding domain suggest that Leu 536 may be involved in hydrophobic interactions at the start of a helix, "helix 12," that is crucial in the **agonist**-stimulated activity of ER.alpha., as well as in the ability of antagonists to block the activity of ER.alpha.. The authors found that certain mutations of Leu 536 increased the ligand-independent activity of ER.alpha. although greatly reducing or eliminating the **agonist** activity of 17.beta.-estradiol (E2) and 4-hydroxytamoxifen (4OHT), on an estrogen response element-driven and an AP-1-driven reporter. The mutations impaired the interaction of the ER ligand-binding domain with the SRC1 receptor-interacting domain in a mammalian two-hybrid system. When tested in the yeast two-hybrid system, mutation of Leu 536 increased the basal reactivity of ER.alpha. to probes that recognize the **agonist**-bound conformation but did not significantly alter its reactivity to these probes in the presence of E2. Most interestingly, mutation of Leu 536 reduced the interaction of the 4OHT-bound ER.alpha. and increased the reactivity of the raloxifene- or ICI 182,780-bound ER.alpha., with probes that recognize the 4OHT-bound ER.alpha. conformation in a yeast two-hybrid system. These results show that Leu 536 is crit. in coupling the binding of ligand to the modulation of the conformation and activity of ER.alpha..

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 16 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:532864 SCISEARCH
THE GENUINE ARTICLE: 689QF
TITLE: The three-dimensional structures of antagonistic and agonistic forms of the glucocorticoid receptor ligand-binding domain - RU-486 induces a transconformation that leads to active antagonism
AUTHOR: Kauppi B (Reprint); Jakob C; Farnegardh M; Yang J; Ahola H; Alarcon M; Calles K; Engstrom O; Harlan J; Muchmore S; Ramqvist A K; Thorell S; Ohman L; Greer J; Gustafsson J A; Carlstedt-Duke J; Carlquist M
CORPORATE SOURCE: Karo Bio AB, Novum, Struct Biol, SE-14157 Huddinge, Sweden (Reprint); Abbott Labs, Dept Biol Struct, Abbott Pk, IL 60064 USA; Huddinge Univ Hosp, Novum, Karolinska Inst, Dept Med Nutr, SE-14157 Huddinge, Sweden; Huddinge Univ Hosp, Novum, Karolinska Inst, Dept Biosci, SE-14157 Huddinge, Sweden
COUNTRY OF AUTHOR: Sweden; USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (20 JUN 2003) Vol. 278, No. 25, pp. 22748-22754.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English

REFERENCE COUNT: 43

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Here we describe the three- dimensional **crystal** structures of human glucocorticoid receptor ligand- binding domain (GR- LBD) in complex with the antagonist RU486 at 2.3 Angstrom resolution and with the **agonist** dexamethasone ligand together with a coactivator peptide at 2.8 Angstrom. The RU- 486 structure was solved in several different **crystal** forms, two with helix 12 intact (GR1 and GR3) and one with a protease- digested C terminus (GR2). In GR1, part of helix 12 is in a position that covers the co- **activator** pocket, whereas in the GR3, domain swapping is seen between the **crystallographically** identical subunits in the GR dimer. An arm consisting of the end of helix 11 and beyond stretches out from one molecule, and helix 12 binds to the other LBD, partly blocking the coactivator pocket of that molecule. This type of GR-LBD dimer has not been described before but might be an artifact from **crystallization**. Furthermore, the subunits of the GR3 dimers are covalently connected via a disulfide bond between the Cys-736 residues in the two molecules. All three RU- 486 GR- LBD structures show that GR has a very flexible region between the end of helix 11 and the end of helix 12.

L15 ANSWER 4 OF 16 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:180330 SCISEARCH

THE GENUINE ARTICLE: 645UK

TITLE: Ligands differentially modulate the protein interactions of the human **estrogen receptors** alpha and beta

AUTHOR: Margeat E; Bourdoncle A; Margueron R; Poujol N; Cavailles V; Royer C (Reprint)

CORPORATE SOURCE: Univ Calif Los Angeles, Dept Chem & Biochem, Los Angeles, CA 90095 USA (Reprint); INSERM, U Endocrinol Mol & Cellulaire Canc 540, F-34090 Montpellier, France; Ctr Biochim Struct, INSERM U554, CNR UMR5048, F-34090 Montpellier, France

COUNTRY OF AUTHOR: USA; France

SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (7 FEB 2003) Vol. 326, No. 1, pp. 77-92.
Publisher: ACADEMIC PRESS LTD ELSEVIER SCIENCE LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND.
ISSN: 0022-2836.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 54

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The interactions of human **estrogen receptor** subtypes ERalpha and ERbeta with DNA and a 210 amino acid residue fragment of the coactivator protein SRC-1 bearing three nuclear receptor interaction motifs were investigated quantitatively using fluorescence anisotropy in the presence of **agonist** and antagonist ligands. ERalpha and ERbeta were found to bind in a similar manner to DNA, and both salt and temperature affected the affinity and/or stoichiometry of these interactions. The **agonist** ligands estradiol, estrone and estriol did not modify the binding of ERalpha to the fluorescein-labeled target estrogen response element. However, in the case of ERbeta, these ligands led to the formation of some higher-order protein-DNA complexes and a small decrease in affinity. The partial **agonist** 4-hydroxytamoxifen had little effect on either ER subtype, whereas the pure antagonist ICI 182,780 led to the cooperative formation of protein-DNA complexes of higher order than dimer, as further demonstrated by competition experiments and gel mobility-shift assays. In addition to DNA binding, the interaction of both ER subtypes with the Alexa488-labeled SRC-1 coactivator fragment was investigated by fluorescence anisotropy. The **agonist** ligands estrone, estradiol, estriol, genistein and ethynyl estradiol exhibited distinct capacities for inducing the recruitment of SRC-1 that were not correlated with their affinity for the receptor. Moreover, estrone and genistein exhibited subtype specificity in that they induced SRC-1 recruitment to ERbeta with much higher efficiency than in the case of ERalpha. The differential coactivator recruitment capacities of the ER **agonists** and their receptor subtype coactivator recruitment specificity may be linked to the molecular

structure of the **agonists** with respect to their interactions with a specific histidine residue located at the back of the ligand-binding pocket. Altogether, these quantitative in vitro studies of ER interactions reveal the complex energetic and stoichiometric consequences of changes in the chemical structures of these proteins and their ligands.

L15 ANSWER 5 OF 16 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:295313 SCISEARCH
THE GENUINE ARTICLE: 534WQ
TITLE: The structural basis for the specificity of retinoid-X receptor-selective **agonists**: New insights into the role of helix H12
AUTHOR: Love J D; Gooch J T; Benko S; Li C; Nagy L; Chatterjee V K K; Evans R M; Schwabe J W R (Reprint)
CORPORATE SOURCE: MRC, Mol Biol Lab, Hills Rd, Cambridge CB2 2QH, England (Reprint); MRC, Mol Biol Lab, Cambridge CB2 2QH, England; Univ Cambridge, Addenbrookes Hosp, Dept Med, Cambridge CB2 2QQ, England; Debrecen Univ, Med & Hlth Sci Ctr, Dept Biochem & Mol Biol, H-4012 Debrecen, Hungary; Salk Inst Biol Studies, Gene Express Lab, La Jolla, CA 92037 USA; Howard Hughes Med Inst, La Jolla, CA 92037 USA
COUNTRY OF AUTHOR: England; Hungary; USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (29 MAR 2002) Vol. 277, No. 13, pp. 11385-11391.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 47
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Ligands that specifically target retinoid-X receptors (RXRs) are emerging as potentially powerful therapies for cancer, diabetes, and the lowering of circulatory cholesterol. To date, RXR has only been **crystallized** in the absence of ligand or with the promiscuous ligand 9-cis retinoic acid, which also activates retinoic acid receptors. Here we present the structure of hRXRbeta in complex with the RXR-specific **agonist** LG100268 (LG268). The structure clearly reveals why LG268 is specific for the RXR ligand binding pocket and will not activate retinoic acid receptors. Intriguingly, in the **crystals**, the C-terminal "activation" helix (AF-2/helix H12) is trapped in a novel position not seen in other nuclear receptor structures such that it does not cap the ligand binding cavity. Mammalian two-hybrid assays indicate that LG268 is unable to release co-repressors from RXR unless co-**activators** are also present. Together these findings suggest that RXR ligands may be inefficient at repositioning helix H12.

L15 ANSWER 6 OF 16 LIFESCI COPYRIGHT 2004 CSA on STN
ACCESSION NUMBER: 2002:68823 LIFESCI
TITLE: Structural characterization of a subtype-selective ligand reveals a novel mode of **estrogen receptor** antagonism
AUTHOR: Shiau, A.K.; Barstad, D.; Radek, J.T.; Meyers, M.J.; Nettles, K.W.; Katzenellenbogen, B.S.; Katzenellenbogen, J.A.; Agard, D.A.; Greene, G.L.
CORPORATE SOURCE: Tularik Inc., Two Corporate Drive, South San Francisco, California 94080, USA; E-mail: ashiau@tularik.com
SOURCE: Nature Structural Biology [Nat. Struct. Biol.], (20020500) vol. 9, no. 5, pp. 359-364.
ISSN: 1072-8368.
DOCUMENT TYPE: Journal
FILE SEGMENT: N
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The R,R enantiomer of 5,11-cis-diethyl-5,6,11,12-tetrahydrochrysene-2,8-diol (THC) exerts opposite effects on the transcriptional activity of the two **estrogen receptor** (ER) subtypes, ER alpha and ER beta . THC acts as an ER alpha **agonist** and as an ER beta antagonist. We have determined the **crystal** structures of the ER

alpha ligand binding domain (LBD) bound to both THC and a fragment of the transcriptional coactivator GRIP1, and the ER beta LBD bound to THC. THC stabilizes a conformation of the ER alpha LBD that permits coactivator association and a conformation of the ER beta LBD that prevents coactivator association. A comparison of the two structures, taken together with functional data, reveals that THC does not act on ER beta through the same mechanisms used by other known ER antagonists. Instead, THC antagonizes ER beta through a novel mechanism we term

L15 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2002:619835 CAPLUS
DOCUMENT NUMBER: 138:180002
TITLE: Pharmacogenomics opportunities in nuclear receptor targeted cancer therapy
AUTHOR(S): Schapira, M.
CORPORATE SOURCE: Department of Pharmacology, New York University School of Medicine, New York, NY, 10016, USA
SOURCE: Current Cancer Drug Targets (2002), 2(3), 243-256
CODEN: CCDTB9; ISSN: 1568-0096
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Nuclear Hormone Receptors (NR) represent one of the most promising protein families in terms of therapeutic applications. These transcription factors are naturally switched on and off by small mol. hormones presenting physico-chem. properties very similar to therapeutic chem. entities. NRs represent therefore intrinsically a very good family of protein targets for the prevention and treatment of diverse diseases, including cancer. Several known anti-cancer drugs, such as tamoxifen or flutamide, are targeting NRs, and many more are expected to reach market. The detailed knowledge of the structural mechanism underlying activation and inhibition of NRs by small mol. modulators begets important therapeutic opportunities. The **crystal** structure of at least nine NR ligand binding domains (LBDs) revealed at the at. level how natural or synthetic **agonists** and antagonists can promote recruitment of co-**activator** and co-repressor proteins. Interestingly, it was recently shown that nucleotide polymorphisms located in NR LBDs could alter or even reverse the response of the receptors to small mol. ligands. Mapping these polymorphisms on the structure of the LBD can reveal why **agonists** or antagonists become inactive against the mutated receptor, allow at. models for resistance to cancer therapy, and open the door to the rational design of improved anti-cancer drugs, customized for each patient.
REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 8 OF 16 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:178579 SCISEARCH
THE GENUINE ARTICLE: 524AU
TITLE: Mass-spectrometric analysis of **agonist**-induced retinoic acid receptor gamma conformational change
AUTHOR: Peterson V J; Barofsky E; Deinzer M L; Dawson M I; Feng K C; Zhang X K; Madduru M R; Leid M (Reprint)
CORPORATE SOURCE: Oregon State Univ, Coll Pharm, Dept Pharmaceut Sci, Mol Pharmacol Lab, Corvallis, OR 97331 USA (Reprint); Oregon State Univ, Dept Chem, Corvallis, OR 97331 USA; Oregon State Univ, Environm Hlth Sci Ctr, Corvallis, OR 97331 USA; Burnham Inst, La Jolla, CA 92037 USA; Rutgers State Univ, Dept Chem, Piscataway, NJ 08854 USA
COUNTRY OF AUTHOR: USA
SOURCE: BIOCHEMICAL JOURNAL, (15 FEB 2002) Vol. 362, Part 1, pp. 173-181.
Publisher: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON W1N 3AJ, ENGLAND.
ISSN: 0264-6021.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 50
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Apo and holo forms of retinoic acid receptors, and other nuclear

receptors, display differential sensitivity to proteolytic digestion that likely reflects the distinct conformational states of the free and liganded forms of the receptor. We have developed a method for rapid peptide mapping of holo-retinoic acid receptor gamma that utilizes matrix-assisted laser-desorption-ionization time-of-flight MS to identify peptide fragments that are derived from the partially proteolysed holo-receptor. The peptide maps of retinoic acid receptor gamma bound by four different **agonists** were identical, suggesting that all four ligands induced a similar conformational change within the ligand-binding domain of the receptor. In all cases, this **agonist**-induced conformational change promoted the direct association of retinoic acid receptor gamma with the transcriptional co-**activator** p300 and inhibited interaction of the receptor with the nuclear receptor co-repressor. SR11253, a compound previously reported to exert mixed retinoic acid receptor gamma **agonist**/antagonist activities in cultured cells, was found to bind directly to, but only weakly altered the protease-sensitivity of, the receptor and failed to promote interaction of the receptor with p300 or induce dissociation of receptor-nuclear receptor corepressor complexes. This technique should be generally applicable to other members of the nuclear receptor superfamily that undergo an induced structural alteration upon **agonist** or antagonist binding, DNA binding and/or protein-protein interaction.

L15 ANSWER 9 OF 16 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:359086 SCISEARCH
THE GENUINE ARTICLE: 670BM
TITLE: Design of thyroid hormone receptor antagonists from first principles
AUTHOR: Webb P (Reprint); Nguyen N H; Chiellini G; Yoshihara H A I; Lima S T C; Apriletti J W; Ribeiro R C J; Marimuthu A; West B L; Goede P; Mellstrom K; Nilsson S; Kushner P J; Fletterick R J; Scanlan T S; Baxter J D
CORPORATE SOURCE: Univ Calif San Francisco, Ctr Diabet, San Francisco, CA 94143 USA (Reprint); Univ Calif San Francisco, Metab Res Unit, San Francisco, CA 94143 USA; Univ Calif San Francisco, Dept Pharmaceut Chem & Mol & Cellular Pharmacol, San Francisco, CA 94143 USA; Karolinska Inst, Novum, Karo Bio AB, S-14157 Huddinge, Sweden; Univ Calif San Francisco, Dept Med, San Francisco, CA 94143 USA; Univ Calif San Francisco, Dept Biochem & Biophys, San Francisco, CA 94143 USA
COUNTRY OF AUTHOR: USA; Sweden
SOURCE: JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY, (DEC 2002) Vol. 83, No. 1-5, pp. 59-73.
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
ISSN: 0960-0760.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 98

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB It is desirable to obtain TR antagonists for treatment of hyperthyroidism and other conditions. We have designed TR antagonists from first principles based on TR **crystal** structures. Since **agonist** ligands are buried in the fold of the TR ligand binding domain (LBD), we reasoned that ligands that resemble **agonists** with large extensions should bind the LBD, but would prevent its folding into an active conformation. In particular, we predicted that extensions at the 5' aryl position of ligand should reposition helix (H) 12, which forms part of the co-**activator** binding surface, and thereby inhibit TR activity. We have found that some synthetic ligands with 5' aryl ring extensions behave as antagonists (DIBRT, NH-3), or partial antagonists (GC-14, NH-4). Moreover, one compound (NH-3) represents the first potent TR antagonist with nanomolar affinity that also inhibits TR action in an animal model. However, the properties of the ligands also reveal unexpected aspects of TR behavior. While nuclear receptor antagonists generally promote binding of co-repressors, NH-3 blocks co-**activator** binding and also prevents co-repressor binding. More surprisingly, many compounds with extensions behave as full or partial **agonists**. We present hypotheses to explain both behaviors in terms

of dynamic equilibrium of H12 position. (C) 2003 Elsevier Science Ltd. All rights reserved.

L15 ANSWER 10 OF 16 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:503310 SCISEARCH
THE GENUINE ARTICLE: 442RC
TITLE: Acyl-CoA esters antagonize the effects of ligands on peroxisome proliferator-activated receptor alpha conformation, DNA binding, and interaction with co-factors
AUTHOR: Elholm R; Dam I; Jorgensen C; Krogsdam A M; Holst D; Kratchmarova I; Gottlicher M; Gustafsson J A; Berge R; Flatmark T; Knudsen J; Mandrup S; Kristiansen K (Reprint)
CORPORATE SOURCE: Univ So Denmark, Dept Biochem & Mol Biol, Campusvej 55, DK-5320 Odense M, Denmark (Reprint); Univ So Denmark, Dept Biochem & Mol Biol, DK-5320 Odense M, Denmark; Univ So Denmark, Ctr Expt Bioinformat, DK-5320 Odense, Denmark; Karolinska Inst, Dept Med Nutr, S-14157 Huddinge, Sweden; Univ Bergen, Inst Clin Biochem, N-5021 Bergen, Norway; Univ Bergen, Dept Biochem & Mol Biol, N-5021 Bergen, Norway
COUNTRY OF AUTHOR: Denmark; Sweden; Norway
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (15 JUN 2001) Vol. 276, No. 24, pp. 21410-21416.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 65
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The peroxisome proliferator-activated receptor alpha (PPAR alpha) is a ligand-activated transcription factor and a key regulator of lipid homeostasis. Numerous fatty acids and eicosanoids serve as ligands and **activators** for PPAR. Here we demonstrate that S-hexadecyl-CoA, a nonhydrolyzable palmitoyl-CoA analog, antagonizes the effects of **agonists** on PPAR alpha conformation and function in vitro, In electrophoretic mobility shift assays, S-hexadecyl-CoA prevented **agonist**-induced binding of the PPAR alpha -retinoid X receptor alpha heterodimer to the acyl-CoA oxidase peroxisome proliferator response element. PPAR alpha bound specifically to immobilized palmitoyl-CoA and Wy14643, but not BRL49653, abolished binding. S-Hexadecyl-CoA increased in a dose-dependent and reversible manner the sensitivity of PPAR alpha to chymotrypsin digestion, and the S-hexadecyl-CoA-induced sensitivity required a functional PPAR alpha ligand-binding pocket. S-Hexadecyl-CoA prevented ligand-induced interaction between the co-**activator** SRC-1 and PPAR alpha but increased recruitment of the nuclear receptor corepressor NCoR, In cells, the concentration of free acyl-CoA esters is kept in the low nanomolar range due to the buffering effect of high affinity acyl-CoA-binding proteins, especially the acyl-CoA-binding protein. By using PPAR alpha expressed in Sf21 cells for electrophoretic mobility shift assays, we demonstrate that S-hexadecyl-CoA was able to increase the mobility of the PPAR alpha -containing heterodimer even in the presence of a molar excess of acyl-CoA-binding protein, mimicking the conditions found in vivo.

L15 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:367826 CAPLUS
DOCUMENT NUMBER: 135:117310
TITLE: **Crystal** structure of a mutant hER.alpha. ligand-binding domain reveals key structural features for the mechanism of partial agonism
AUTHOR(S): Gangloff, Monique; Ruff, Marc; Eiler, Sylvia; Duclaud, Sylvie; Wurtz, Jean Marie; Moras, Dino
CORPORATE SOURCE: Institut de Genetique et de Biologie Moleculaire et Cellulaire, Laboratoire de Biologie et de Genomique Structurales, Illkirch, 67404, Fr.
SOURCE: Journal of Biological Chemistry (2001), 276(18), 15059-15065
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular

Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **crystal** structure of a triple cysteine to serine mutant ER.alpha. ligand-binding domain (LBD), complexed with estradiol, shows that despite the presence of a tightly bound **agonist** ligand, the protein exhibits an antagonist-like conformation, similar to that obsd. in raloxifen and 4-hydroxytamoxifen-bound structures. This mutated receptor binds estradiol with wild type affinity and displays transcriptional activity upon estradiol stimulation, but with limited potency (about 50%). This partial activity is efficiently repressed in antagonist competition assays. The comparison with available LBD structures reveals key features governing the positioning of helix H12 and highlights the importance of cysteine residues in promoting an active conformation. Furthermore the present study reveals a hydrogen bond network connecting ligand binding to protein trans conformation. These observations support a dynamic view of H12 positioning, where the control of the equil. between two stable locations dets. the partial **agonist** character of a given ligand.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 12 OF 16 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:373497 SCISEARCH
THE GENUINE ARTICLE: 427NL
TITLE: Molecular mechanisms of retinoid action
AUTHOR: Gronemeyer H (Reprint); Miturski R
CORPORATE SOURCE: ULP, CNRS, INSERM, IGBMC, BP 163, F-67404 Illkirch, CU Strasbourg, France (Reprint); ULP, CNRS, INSERM, IGBMC, F-67404 Illkirch, CU Strasbourg, France; Med Univ, Dept Gynaecol Surg 2, Lublin, Poland
COUNTRY OF AUTHOR: France; Poland
SOURCE: CELLULAR & MOLECULAR BIOLOGY LETTERS, (FEB 2001) Vol. 6, No. 1, pp. 3-52.
Publisher: CELLULAR & MOLECULAR BIOLOGY LETTERS, UNIV WROCLAW, INST BIOCHEM, DEPT GENETIC BIOCHEMISTRY, PRZBYSZEWSKIEGO 63/77, 51-148 WROCLAW, POLAND.
ISSN: 1425-8153.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 203

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In the past few years our understanding of nuclear receptor (NR) action has been dramatically improved. This is due to to advancements in three fields, (i) 3D structure determination, (ii) analysis of the complexes formed between nuclear receptors and co-regulatory molecules, and (iii) the genetic analysis of nuclear receptor signalling by gene "knock out" and "knock in" technologies. The elucidation of the **crystal** structure of apo-, hole (**agonist**)- and antagonist-NR ligand-binding domain (LBD) complexes is of outstanding importance for our understanding of the structural principles, in particular of the ligand-induced allosteric alterations, that are at the basis of receptor action. The concomitant identification and functional analysis of co-regulators (TIFs, co-**activators** and co-repressors) previously predicted from squelching studies have provided the possibility to understand the propagation of the original signal from ligand binding through intramolecular allosteric effects to intermolecular interactions. Recent **crystal** data of receptor LED heterodimers and LBD-**agonist** complexes with nuclear receptor interacting peptides of co-**activators** have provided molecular insights into receptor dimerization and receptor-coactivator interaction, Finally, analysis of the signalling compexes established over nuclear receptors, assembling enzymatic activities that can alter the acetylation status of chromatin at the promoter regions of target genes and (de)acetylate other transcription regulatory factors paves the way to a comprehension of receptor action at the chromatin level. But much remains to be learnt and the recent studies have pointed towards an enormous complexity of this signalling system. Insights into the mechanistic basis of promyelocytic leukemia and the role of retinoic acid in differentiation therapy have been obtained as a consequence of the above studies, justified the efforts and led to an increasing awareness of the nuclear receptor signalling systems in basic

and applied research. Here we will review recent data with the focus on what we have learnt about the interplay between NR structure and function to provide a view of the early steps of nuclear receptor action.

L15 ANSWER 13 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2000403373 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10935307
TITLE: [Specific modulators of estrogen action].
Les modulateurs specifiques de l'action des oestrogenes.
AUTHOR: Guiochon-Mantel A
CORPORATE SOURCE: Inserm U 135, laboratoire d'hormonologie et biologie moleculaire, hopital de Bicetre, Le Kremlin, France.
SOURCE: Gynecologie, obstetrique & fertilite, (2000 Jun) 28 (6) 429-34. Ref: 33
Journal code: 100936305. ISSN: 1297-9589.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000901
Last Updated on STN: 20000901
Entered Medline: 20000822

AB Selective estradiol receptor modulators (SERMs) are specific modulators of estradiol action. They are used in therapeutics to obtain an estrogenic effect on certain cells and an antiestrogenic effect on other cells. Recent progress in the knowledge of the mechanism of action of estradiols implies that new molecules could be designed. This progress involves the cloning of a new estradiol receptor, ER beta, the discovery of co-**activators** and the elucidation of their molecular mechanism of action, and the **crystallization** of the ligand binding domain in the presence of an **agonist** or an antagonist.

L15 ANSWER 14 OF 16 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2000482719 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10971099
TITLE: Selective oestrogen receptor modulators.
AUTHOR: Burger H G
CORPORATE SOURCE: Prince Henry's Institute of Medical Research, Monash Medical Centre, Clayton, Vic., Australia.
SOURCE: Hormone research, (2000) 53 Suppl 3 25-9. Ref: 15
Journal code: 0366126. ISSN: 0301-0163.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001019
Last Updated on STN: 20001019
Entered Medline: 20001011

AB Selective oestrogen receptor modulators (SERMs) are compounds which act like oestrogens in some target tissues but which antagonise their effects in others. The first example of a SERM (referred to as a first-generation compound) was tamoxifen, for which oestrogen-like **agonist** activity on bone was seen to occur simultaneously with oestrogen antagonist activity on the breast. An unwanted effect of tamoxifen was its oestrogen-like action on the endometrium. Second-generation compounds have since been developed, most notably raloxifene, which has oestrogen-like actions on bone, lipids and the coagulation system, and oestrogen antagonist effects on the breast and uterus. Raloxifene has undergone very extensive, prospective, placebo-controlled, randomised trial evaluation, in which anti-fracture efficacy (to date only for vertebral fracture) has been accompanied by a major reduction in the incidence of new breast cancer. The compound is similar to placebo in its uterine effects, and similar to oestrogen in causing a two- to threefold increase in the risk of venous thromboembolism. Its lipid effects are similar to those of oestrogen, except for a relatively small effect on

high-density lipoprotein cholesterol, and no significant effect on triglycerides. Data on cardiovascular event rates are not yet available; data on cognitive function are preliminary and, to date, reassuring. The mechanisms by which the same compound can exert oestrogen **agonist** effects on one target and antagonist effects on another are still being clarified. Important aspects include the fact that the oestrogen receptor undergoes different conformational changes according to the ligand. Thus the **crystal** structure of oestradiol bound to the oestrogen receptor differs from that of raloxifene bound to the same receptor. The existence of two oestrogen receptor subtypes may also be relevant. Mechanisms include differing interactions with various domains of the oestrogen receptor, and tissue-specific recruitment of steroid receptor co-**activators** and co-repressors may underlie some of the tissue-specific effects. The SERMs may be the prototype for other selective steroid receptor modulators, for example the androgen and progesterone receptors. The development of tissue target-specific agents is an exciting advance in endocrine pharmacology and can be extended to agents, such as tibolone, which exert some of their tissue specificity through their metabolites.

L15 ANSWER 15 OF 16 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2000:435213 BIOSIS
DOCUMENT NUMBER: PREV200000435213
TITLE: Selective oestrogen receptor modulators.
AUTHOR(S): Burger, Henry G. [Reprint author]
CORPORATE SOURCE: Prince Henry's Institute of Medical Research, Monash Medical Centre, Clayton, VIC, 3168, Australia
SOURCE: Hormone Research (Basel), (August, 2000) Vol. 50, No. Suppl. 3, pp. 25-29. print.
CODEN: HRMRA3. ISSN: 0301-0163.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Oct 2000
Last Updated on STN: 10 Jan 2002

AB Selective oestrogen receptor modulators (SERMs) are compounds which act like oestrogens in some target tissues but which antagonise their effects in others. The first example of a SERM (referred to as a first-generation compound) was tamoxifen, for which oestrogen-like **agonist** activity on bone was seen to occur simultaneously with oestrogen antagonist activity on the breast. An unwanted effect of tamoxifen was its oestrogen-like action on the endometrium. Second-generation compounds have since been developed, most notably raloxifene, which has oestrogen-like actions on bone, lipids and the coagulation system, and oestrogen antagonist effects on the breast and uterus. Raloxifene has undergone very extensive, prospective, placebo-controlled, randomised trial evaluation, in which anti-fracture efficacy (to date only for vertebral fracture) has been accompanied by a major reduction in the incidence of new breast cancer. The compound is similar to placebo in its uterine effects, and similar to oestrogen in causing a two- to threefold increase in the risk of venous thromboembolism. Its lipid effects are similar to those of oestrogen, except for a relatively small effect on high-density lipoprotein cholesterol, and no significant effect on triglycerides. Data on cardiovascular event rates are not yet available; data on cognitive function are preliminary and, to date, reassuring. The mechanisms by which the same compound can exert oestrogen **agonist** effects on one target and antagonist effects on another are still being clarified. Important aspects include the fact that the oestrogen receptor undergoes different conformational changes according to the ligand. Thus the **crystal** structure of oestradiol bound to the oestrogen receptor differs from that of raloxifene bound to the same receptor. The existence of two oestrogen receptor subtypes may also be relevant. Mechanisms include differing interactions with various domains of the oestrogen receptor, and tissue-specific recruitment of steroid receptor co-**activators** and co-repressors may underlie some of the tissue-specific effects. The SERMs may be the prototype for other selective steroid receptor modulators, for example the androgen and progesterone receptors. The development of tissue target-specific agents is an exciting advance in endocrine pharmacology and can be extended to agents, such as tibolone, which exert some of their tissue specificity

through their metabolites.

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=> s estrogen receptor and agonist and coactivator
TOTAL FOR ALL FILES
L22        580 ESTROGEN RECEPTOR AND AGONIST AND COACTIVATOR

=> s l22 and crystal?
TOTAL FOR ALL FILES
L29         74 L22 AND CRYSTAL?

=> s l29 not 2000-2004/py
TOTAL FOR ALL FILES
L36         10 L29 NOT 2000-2004/PY

=> dup rem l36
PROCESSING COMPLETED FOR L36
L37          5 DUP REM L36 (5 DUPLICATES REMOVED)

=> d ibib abs

L37  ANSWER 1 OF 5     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:   1999091051     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 9875847
TITLE:              The structural basis of estrogen receptor
                    /coactivator recognition and the antagonism of
                    this interaction by tamoxifen.
AUTHOR:             Shiau A K; Barstad D; Loria P M; Cheng L; Kushner P J;
                    Agard D A; Greene G L
CORPORATE SOURCE:   Howard Hughes Medical Institute and the Department of
                    Biochemistry and Biophysics, University of California at
                    San Francisco, 94143-0448, USA.
CONTRACT NUMBER:    DK51083 (NIDDK)
     GM31627 (NIGMS)
     P30 CA-14599 (NCI)
SOURCE:             Cell, (1998 Dec 23) 95 (7) 927-37.
                    Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
OTHER SOURCE:       PDB
ENTRY MONTH:        199901
ENTRY DATE:         Entered STN: 19990202
                    Last Updated on STN: 19990202
                    Entered Medline: 19990119
AB   Ligand-dependent activation of transcription by nuclear receptors (NRs) is
     mediated by interactions with coactivators. Receptor
     agonists promote coactivator binding, and antagonists
     block coactivator binding. Here we report the crystal
     structure of the human estrogen receptor alpha (hER
     alpha) ligand-binding domain (LBD) bound to both the agonist
     diethylstilbestrol (DES) and a peptide derived from the NR box II region
     of the coactivator GRIP1 and the crystal structure of
     the hER alpha LBD bound to the selective antagonist 4-hydroxytamoxifen
     (OHT). In the DES-LBD-peptide complex, the peptide binds as a short alpha
     helix to a hydrophobic groove on the surface of the LBD. In the OHT-LBD
     complex, helix 12 occludes the coactivator recognition groove by
     mimicking the interactions of the NR box peptide with the LBD. These
     structures reveal the two distinct mechanisms by which structural features
     of OHT promote this "autoinhibitory" helix 12 conformation.


=> d ibib abs 2-5

L37  ANSWER 2 OF 5  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
ACCESSION NUMBER:   1998222281  EMBASE
TITLE:              Basic guide to the mechanisms of antiestrogen action.
AUTHOR:             Macgregor J.I.; Jordan V.C.
CORPORATE SOURCE:   V.C. Jordan, Robert H. Lurie Compreh. Can. Ctr., 8258 Olsen
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Pavilion, Northwestern Univ. Medical School, 303 East Chicago Ave., Chicago, IL 60611, United States
SOURCE: Pharmacological Reviews, (1998) 50/2 (151-196).
Refs: 540
ISSN: 0031-6997 CODEN: PAREAQ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Forty years ago, Lerner and coworkers (1958) discovered the first nonsteroidal antiestrogen and Jensen (Jensen and Jacobson, 1960) identified a target for drug action, the ER. This knowledge opened the door for the clinical development of tamoxifen which we now know provides a survival advantage in both node-positive and node-negative patients with ER-positive disease (Early. Breast Cancer Trialists Collaborative Group, 1992, 1998). The drug has been studied extensively, and the results have provided an invaluable insight into possible ancillary advantages of 'antiestrogens', i.e., maintenance of bone density and the prevention of coronary heart disease, and possible disadvantages, i.e., rat liver carcinogenesis and an increased risk of endometrial cancer. Most importantly, the identification of the target site-specific actions of tamoxifen caused a paradigm shift in the prospective uses of antiestrogens from a direct exploitation of the antitumor properties to the broader application as a preventative for osteoporosis, but with the beneficial side effects of preventing breast and endometrial cancer. Raloxifene, a second-generation SERM, has all the properties in the laboratory that would encourage development as a safe preventative for osteoporosis (Jordan et al., 1997). As a result, raloxifene has been evaluated in more than 11,000 postmenopausal women and found to maintain bone density with significant decreases in breast cancer incidence and no increase in endometrial thickness. Raloxifene is now available as a preventative for osteoporosis in postmenopausal women. There is every reason to believe that a multifaceted agent like raloxifene will find widespread use, and there will be continuing interest by the pharmaceutical industry in the development of new agents with even broader applications. The extensive clinical effort is augmented by past molecular innovations in the laboratory and the future promise of new discoveries. The cloning and sequencing of the ER (Green et al., 1986; Greene et al., 1986) has allowed the development of an ER knock- out mouse (Lubahn et al., 1993) that compliments Jensen's pioneering work (Jensen and Jacobson, 1962) and describes the consequences of the loss of ER.alpha.. However, ER.beta. (Kuiper et al., 1996), the second ER, has provided an additional dimension to the description of estrogen and antiestrogen action. For the future, the development of ER.beta. monoclonal antibodies, the classification of target sites for the protein around the body, and the creation of ER.beta. and ER.alpha.,.beta. knock-out mice will identify new therapeutic targets to modulate physiological functions. Clearly, the successful **crystallization** of ER.alpha. with raloxifene (Brzozowski et al., 1997) must act as a stimulus for the **crystallization** of ER.beta.. The central issue for research on antiestrogen pharmacology is the discovery of the mechanism (or mechanisms) of target site-specificity for the modulation of estrogenic and antiestrogenic response. The description of a stimulatory pathway for antiestrogens through an AP-1 ER.beta. signal transduction pathway (Paech et al., 1997), although interesting, may not entirely explain the estrogenicity of antiestrogens. The model must encompass the sum of pharmacological consequences of signal transduction through ER.alpha. and ER.beta. with the simultaneous competition from endogenous estrogens at both sites. This is complicated because estradiol is an antagonist at ER.beta. through AP-1 sites (Paech et al., 1997), so this is clearly not the pathway for estrogen- induced bone maintenance in women. Estrogen is stimulatory through ER.alpha., but antiestrogens are usually partial **agonists** and may either block or stimulate genes. However, we suggest that the ER.alpha. stimulatory pathway could be amplified through selective increases in **coactivators**. The principle is illustrated with the MDA-MB-231 cells stably transfected with the cDNAs for the wild-type and the amino acid 351 mutant receptors (Jiang and Jordan, 1992; Catherino et al.,

1995). Raloxifene has increased estrogenicity with the mutant ER transfectant compared with the transfectants containing wild- type ER where the pharmacology of raloxifene is a complete antiestrogen (fig. 21). By contrast,. 4-OHT is a complete estrogen with the wild-type ER transfectants stimulating expression of the TGF.alpha. gene, and the response is amplified further in transfectants with the cDNA from the amino acid 351 mutant ER (fig. 22) (Levenson et al., 1998). The 4-OHT-ER complex is clearly different than the raloxifene-ER complex. This confirms the suggestions by McDonnell and colleagues (1995) that the ligand-receptor complexes can display a range of conformations. We suggest that the reason for the promiscuity of the 4-OHT-ER complex in the transfectants is an increased level of **coactivator** in breast cancer cells that were originally ER negative. If the **coactivators** can provoke transcription with the wild-type 4-OHT-ER complex, then the orientation of the H12 helix must be different than that observed with the **crystal** structure of raloxifene. Indeed, it is possible that there are several conformations in equilibrium so that a single **crystal** shape alone will not describe the spectrum of tamoxifen's actions. This hypothesis could explain the development of tamoxifen-stimulated breast cancer. Receptor-positive cells that contain an excess of transcription factors and **coactivators** would be selected through a growth advantage during tamoxifen therapy. The laboratory models of tamoxifen-stimulated breast cancer are, therefore, a valuable reproducible resource to test the hypothesis. Techniques are available to identify the **coactivators** for the ER. However, we suggest that a solution of the molecular mechanism of antiestrogen-stimulated growth will not only solve a problem of drug resistance but also may provide an insight into the target site-specific actions of antiestrogens.

L37 ANSWER 3 OF 5 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1998:841894 SCISEARCH
THE GENUINE ARTICLE: 133LB
TITLE: Molecular and structural biology of thyroid hormone receptors
AUTHOR: Apriletti J W (Reprint); Ribeiro R C J; Wagner R L; Feng W; Webb P; Kushner P J; West B L; Nilsson S; Scanlan T S; Fletterick R J; Baxter J D
CORPORATE SOURCE: UNIV CALIF SAN FRANCISCO, METAB RES UNIT, SAN FRANCISCO, CA 94143 (Reprint); UNIV CALIF SAN FRANCISCO, DEPT BIOCHEM & BIOPHYS, SAN FRANCISCO, CA 94143; UNIV CALIF SAN FRANCISCO, DEPT PHARMACEUT CHEM, SAN FRANCISCO, CA 94143; UNIV CALIF SAN FRANCISCO, DEPT CELLULAR & MOL PHARMACOL, SAN FRANCISCO, CA 94143; UNIV BRASILIA, DEPT PHARMACEUT SCI, BRASILIA, DF, BRAZIL; KAO BIO AB, HUDDINGE, SWEDEN
COUNTRY OF AUTHOR: USA; BRAZIL; SWEDEN
SOURCE: CLINICAL AND EXPERIMENTAL PHARMACOLOGY AND PHYSIOLOGY, (NOV 1998) Vol. 25, Supp. [S], pp. S2-S11.
Publisher: BLACKWELL SCIENCE, 54 UNIVERSITY ST, P O BOX 378, CARLTON VICTORIA 3053, AUSTRALIA.
ISSN: 0305-1870.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 45

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB 1. Thyroid hormone receptors (TR) are expressed from two separate genes (alpha and beta) and belong to the nuclear receptor superfamily, which also contains receptors for steroids, vitamins and prostaglandins.

2. Unliganded TR are bound to DNA thyroid hormone response elements (TRE) predominantly as homodimers, or as heterodimers with retinoid X-receptors (RXR), and are associated with a complex of proteins containing corepressor proteins, Ligand binding promotes corepressor dissociation and binding of a **coactivator**.

3. Recent studies from our group have focused on the acquisition and use of X-ray **crystallographic** structures of ligand-binding domains (LBD) of both the rat (r) TR alpha and the human (h) TR beta bound to several different ligands. We have also developed ligands that bind selectively to the TR beta, which may provide ways to explore the differential functions of TR alpha compared with TR beta isoforms,

4. The LED is comprised mostly of alpha-helices, The ligand is

completely buried in the receptor and forms part of its hydrophobic core. Kinetic studies suggest that the limiting step in formation of high-affinity Ligand-receptor complexes is the rate of folding of the receptor around the ligand, Ligands can be fitted tightly in the ligand-binding pocket and small differences in this fitting may explain many structure-activity relationships. Interestingly, analysis of the structures of antagonists suggests that they have chemical groups, 'extensions', that could impair receptor folding around them and, thus, prevent the **agonist**-induced conformation changes in the receptor.

5. The TR structures allowed us to see that the mutations that occur in the syndrome of generalized resistance to thyroid hormone are located in the vicinity of the ligand-binding pocket.

6. X-ray structure of the TR has also been used to guide construction of mutations in the TR surface that block binding of various proteins important for receptor function. Studies with these TR mutants reveal that the interfaces for homo- and heterodimerization map to similar residues in helix 10 and 11 and also allow the definition of the surface for binding of **coactivators**, which appears to be general for nuclear receptors, Formation of this surface, which involves packing of helix 12 of the TR into a scaffold formed by helices 3 and 5, appears to be the major change in the receptor structure induced by hormone occupancy.

L37 ANSWER 4 OF 5 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 97:346843 SCISEARCH
THE GENUINE ARTICLE: WW609
TITLE: **Estrogen receptor** residues required for stereospecific ligand recognition and activation
AUTHOR: Bocchinfuso W P; Korach K S (Reprint)
CORPORATE SOURCE: NIEHS, RECEPTOR BIOL SECT, REPROD & DEV TOXICOL LAB, NIH, MD B3-01, POB 12233, RES TRIANGLE PK, NC 27709 (Reprint); NIEHS, RECEPTOR BIOL SECT, REPROD & DEV TOXICOL LAB, NIH, RES TRIANGLE PK, NC 27709
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR ENDOCRINOLOGY, (MAY 1997) Vol. 11, No. 5, pp. 587-594.
Publisher: ENDOCRINE SOC, 4350 EAST WEST HIGHWAY SUITE 500, BETHESDA, MD 20814-4110.
ISSN: 0888-8809.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The mouse **estrogen receptor** (mER) has been shown to exhibit stereospecific binding of certain stilbene estrogen **agonists**. The region of the mER involved in the stereochemical recognition of ligands was further defined using a stilbene isomer, Indenestrol B (IB). The IB compound has a chiral carbon bearing an ethyl substituent, and the wild type uterine mER has been shown to bind the enantiomers, IB-S and IB-R, with similar affinity. The wild type mER expressed in yeast exhibited a very minor preference for IB-S in transactivation (1.5-fold lower half-maximal dose than IB-R). The IB enantiomers could then be used to determine whether stereochemically distinct compounds with similar transcriptional activity utilize different amino acids in AF-2 for transactivation. Mutant mERs with glycine substitutions at Met521, His528, Met532, and Val537 were expressed in yeast and measured for IB-S- and IB-R-induced transactivation and ligand binding. The M532G mER showed a 124-fold and 50-fold reduction in transactivation induced by IB-S and IB-R, respectively, without a corresponding change in their ligand-binding affinities. Therefore, Met532 is required for transactivation induced by both IB enantiomers but does not discriminate based on stereospecificity. In contrast, the H528G mER displayed a gross change in stereospecific ligand recognition as illustrated by a 110-fold reduction in transactivation by IB-S and only a 8.8-fold decrease in activity by IB-R. As a result, H528G mER displayed a switch in ligand preference such that IB-R was now 8-fold more active than IB-S in transactivation. Therefore, His528 appears largely involved in transactivation specifically induced by IB-S but has a minimal influence in IB-S ligand binding. The remaining mutant mERs displayed wild type

ligand binding and transactivation properties for the IB enantiomers illustrating no stereospecific recognition. These results imply that individual IB enantiomers bind to the mER with similar affinity but utilize at least one different amino acid within the AF-2 domain for signal transduction. The binding of stereochemically distinct ligands may alter the tertiary structure of the mER and cause repositioning of the AF-2 region that mediates transcription of specific genes and/or affect the binding of receptor-associated proteins, such as **coactivators** , which could influence transcription.

L37 ANSWER 5 OF 5 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 97:121445 SCISEARCH
THE GENUINE ARTICLE: WF111
TITLE: RIP 140 enhances nuclear receptor-dependent transcription in vivo in yeast
AUTHOR: Joyeux A; Cavailles V; Balaguer P; Nicolas J C (Reprint)
CORPORATE SOURCE: INSERM, U439, 70 RUE NAVACELLES, F-34090 MONTPELLIER, FRANCE (Reprint); INSERM, U439, F-34090 MONTPELLIER, FRANCE; INSERM, U148, F-34090 MONTPELLIER, FRANCE
COUNTRY OF AUTHOR: FRANCE
SOURCE: MOLECULAR ENDOCRINOLOGY, (FEB 1997) Vol. 11, No. 2, pp. 193-202.
Publisher: ENDOCRINE SOC, 4350 EAST WEST HIGHWAY SUITE 500, BETHESDA, MD 20814-4110.
ISSN: 0888-8809.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 62

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB RIP140 has previoulsy been cloned as a factor that interacts with the **estrogen receptor** (ER) in vitro. We demonstrate in this study that RIP140 is a cofactor for nuclear receptor in yeast. RIP140 enhances the ER transcriptional activity by increasing 1.5- to 4-fold the induction factor of the reporter gene response at saturating hormone concentrations, this effect being magnified at suboptimal doses of estradiol. Moreover, RIP140 decreases the ED(50) of the dose-response curve. These effects are recovered with an N-terminal truncated ER, but impaired by point mutations that abolish AFP-AD activity. We did not observe any modulation of the partial **agonist** 4-hydroxytamoxifen activity in the presence of RIP140, Thus, RIP140 modulates transcriptional activity of ER through the AFP-AD domain and in a **agonist** -dependent fashion. RIP140 is also a strong **coactivator** for the retinoid pathway, as its expression enhances 10-fold the transactivation of a chimeric retinoic acid-alpha receptor at saturant hormone concentration and left shifted 5-fold the ED(50) of the dose-response curve. We have investigated whether RIP140 could be involved in cross-talk between estrogenic and retinoid pathways.

=> log y

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Thursday, November 18, 2004

Hide?	Set Name	Query	Hit Count
	DB=PGPB; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L4	L3 and crystal?	16
☐	L3	estrogen receptor same (agonist or diethylstilbestrol or DES) same (activator or coactivator)	49
	DB=USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L2	L1 and crystal?	6
☐	L1	estrogen receptor same (agonist or diethylstilbestrol or DES) same (activator or coactivator)	25

END OF SEARCH HISTORY

Hit List

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Search Results - Record(s) 1 through 6 of 6 returned.

☐ 1. Document ID: US 6667299 B1

Using default format because multiple data bases are involved.

L2: Entry 1 of 6 File: USPT Dec 23, 2003

US-PAT-NO: 6667299
DOCUMENT-IDENTIFIER: US 6667299 B1

TITLE: Pharmaceutical compositions and treatment methods

DATE-ISSUED: December 23, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ahlem; Clarence Nathaniel	San Diego	CA		
de Carvalho; Luis Daniel dos Anjos	Paio Pires			PT
Heggie; William	Palmela			PT

US-CL-CURRENT: 514/178; 552/536

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

☐ 2. Document ID: US 6616869 B2

L2: Entry 2 of 6 File: USPT Sep 9, 2003

US-PAT-NO: 6616869
DOCUMENT-IDENTIFIER: US 6616869 B2

TITLE: Process for preparing microparticles through phase inversion phenomena

DATE-ISSUED: September 9, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mathiowitz; Edith	Brookline	MA		
Chickering, III; Donald	Pfulgerville	TX		
Jong; Yong S.	Warwick	RI		
Jacob; Jules S.	Taunton	MA		

US-CL-CURRENT: 264/4; 264/4.1, 427/213.36

ABSTRACT:

A process for preparing nanoparticles and microparticles is provided. The process involves forming a mixture of a polymer and a solvent, wherein the solvent is present in a continuous phase and introducing the mixture into an effective amount of a nonsolvent to cause the spontaneous formation of microparticles.

37 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

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☐ 3. Document ID: US 6545049 B1

L2: Entry 3 of 6 File: USPT Apr 8, 2003

US-PAT-NO: 6545049
DOCUMENT-IDENTIFIER: US 6545049 B1

TITLE: Dimer-selective RXR modulators and methods for their use

DATE-ISSUED: April 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Canan-Koch; Stacie	San Diego	CA		
Hwang; Chan K.	Boulder	CO		
Boehm; Marcus F.	San Diego	CA		
Badea; Beth Ann	San Diego	CA		
Dardashti; Laura J.	Santa Anna	CA		
Zhang; Lin	San Diego	CA		
Nadzan; Alex M.	San Diego	CA		
Heyman; Richard A.	Encinitas	CA		
Mukherjee; Ranjan	San Diego	CA		
Lala; Deepak S.	San Diego	CA		
Farmer; Luc J.	La Jolla	CA		

US-CL-CURRENT: 514/569; 514/725, 560/58

ABSTRACT:

Dimer-selective RXR modulator compounds having agonist, partial agonist and/or antagonist activity in the context of an RXR homodimer and/or RXR heterodimers are provided. Also provided are pharmaceutical compositions incorporating such dimer-selective RXR modulator compounds and methods for their therapeutic use.

36 Claims, 6 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 4. Document ID: US 6235224 B1

L2: Entry 4 of 6 File: USPT May 22, 2001

US-PAT-NO: 6235224
DOCUMENT-IDENTIFIER: US 6235224 B1
**** See image for Certificate of Correction ****

TITLE: Process for preparing microparticles through phase inversion phenomena

DATE-ISSUED: May 22, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mathiowitz; Edith	Brookline	MA		
Chickering, III; Donald	Pfulgerville	TX		
Jong; Yong S.	Warwick	RI		
Jacob; Jules S.	Taunton	MA		

US-CL-CURRENT: 264/4; 264/4.1, 427/213.36

ABSTRACT:

A process for preparing nanoparticles and microparticles is provided. The process involves forming a mixture of a polymer and a solvent, wherein the solvent is present in a continuous phase and introducing the mixture into an effective amount of a nonsolvent to cause the spontaneous formation of microparticles.

4 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 5. Document ID: US 6218128 B1

L2: Entry 5 of 6 File: USPT Apr 17, 2001

US-PAT-NO: 6218128
DOCUMENT-IDENTIFIER: US 6218128 B1
**** See image for Certificate of Correction ****

TITLE: Methods of identifying compounds having nuclear receptor negative hormone and/or antagonist activities

DATE-ISSUED: April 17, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Klein; Elliott S.	Marina Del Rey	CA
Nagpal; Sunil	Lake Forest	CA
Chandraratna; Roshantha A.	Mission Viejo	CA

US-CL-CURRENT: 435/7.1

ABSTRACT:

Methods of characterizing and identifying negative hormones of nuclear receptors. Also disclosed are methods of making modulators of retinoid nuclear receptor transactivation activity, assays for agonists, antagonists, and negative hormones of the RAR receptor, and specific retinoid modulators of retinoid nuclear receptors.

21 Claims, 30 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 20

☐ 6. Document ID: US 6143211 A

L2: Entry 6 of 6 File: USPT Nov 7, 2000

US-PAT-NO: 6143211
DOCUMENT-IDENTIFIER: US 6143211 A
**** See image for Certificate of Correction ****

TITLE: Process for preparing microparticles through phase inversion phenomena

DATE-ISSUED: November 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mathiowitz; Edith	Brookline	MA		
Chickering, III; Donald	Pfulgerville	TX		
Jong; Yong S.	Warwick	RI		
Jacob; Jules S.	Taunton	MA		

US-CL-CURRENT: 264/4; 264/4.1, 427/213.36

ABSTRACT:

A process for preparing nanoparticles and microparticles is provided. The process involves forming a mixture of a polymer and a solvent, wherein the solvent is present in a continuous phase and introducing the mixture into an effective amount of a nonsolvent to cause the spontaneous formation of microparticles.

31 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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Terms	Documents
L1 and crystal?	6

Display Format: - Change Format

Previous Page Next Page Go to Doc#

Hit List

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 1 through 20 of 25 returned.

☐ 1. Document ID: US 6812336 B1

Using default format because multiple data bases are involved.

L1: Entry 1 of 25 File: USPT Nov 2, 2004

US-PAT-NO: 6812336
DOCUMENT-IDENTIFIER: US 6812336 B1

TITLE: Transcription factor coactivator protein, p/CIP

DATE-ISSUED: November 2, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rosenfeld; Michael G.	San Diego	CA		
Glass; Christopher K.	San Diego	CA		
Rose; David W.	San Diego	CA		
Torchia; Joseph	London			CA

US-CL-CURRENT: 536/23.5; 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 2. Document ID: US 6770620 B2

L1: Entry 2 of 25 File: USPT Aug 3, 2004

US-PAT-NO: 6770620
DOCUMENT-IDENTIFIER: US 6770620 B2

TITLE: Use of GLP for the treatment, prevention, diagnosis, and prognosis of bone-related and nutrition-related disorders

DATE-ISSUED: August 3, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Henriksen; Dennis Bang	Alleroed			DK

US-CL-CURRENT: 514/2; 514/102, 514/108, 514/12, 530/308, 530/324

ABSTRACT:

The present invention relates to methods for prevention and treatment of bone-related or nutrition-related disorders using a GLP molecule or GLP activator either alone or in combination with another therapeutic. The present invention also encompasses methods of diagnosing or monitoring the progression of a disorder. The invention also encompasses methods of monitoring the effectiveness of treatment of the invention.

3 Claims, 5 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

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☐ 3. Document ID: US 6746635 B2

L1: Entry 3 of 25 File: USPT Jun 8, 2004

US-PAT-NO: 6746635
DOCUMENT-IDENTIFIER: US 6746635 B2

TITLE: Methods for micronization of hydrophobic drugs

DATE-ISSUED: June 8, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mathiowitz; Edith	Brookline	MA		
Thanos; Christopher	Providence	RI		
Liu; Zhi	West Roxbury	MA		

US-CL-CURRENT: 264/4.3; 264/4.1, 264/4.6

ABSTRACT:

The invention involves methods and products related to the micronization of hydrophobic drugs. A method of micronizing hydrophobic drugs using a set of solutions including an aqueous solution is provided. The invention also relates to products of micronized hydrophobic drugs and related methods of use.

13 Claims, 21 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

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☐ 4. Document ID: US 6693170 B2

L1: Entry 4 of 25 File: USPT Feb 17, 2004

US-PAT-NO: 6693170
DOCUMENT-IDENTIFIER: US 6693170 B2

TITLE: ARIP4 gene and protein

DATE-ISSUED: February 17, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rouleau; Nathalie	Montreal, P.Q.		H2H 2A1	CA
Moilanen; Anu-Maarit	Turku		FIN-20720	FI
Palvimo; Jorma J.	Helsinki		FIN-00820	FI
Janne; Olli A.	Espoo		FIN-02160	FI

US-CL-CURRENT: 530/350; 435/196, 530/300, 530/326, 530/327

ABSTRACT:

This invention relates to a novel nuclear protein which interacts with the androgen receptor in vivo and in vitro, and which also possesses ATPase activity. The invention concerns also mRNA and DNA sequences encoding said protein.

4 Claims, 7 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 7

☐ 5. Document ID: US 6689574 B1

L1: Entry 5 of 25 File: USPT Feb 10, 2004

US-PAT-NO: 6689574
DOCUMENT-IDENTIFIER: US 6689574 B1

TITLE: Assays for nuclear receptor agonists and antagonists using fluorescence resonance energy transfer

DATE-ISSUED: February 10, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cummings; Richard T.	Fanwood	NJ		
Moller; David E.	Watchung	NJ		
Hermes; Jeffrey D.	Warren	NJ		
Zhou; Gaochao	Scotch Plains	NJ		

US-CL-CURRENT: 435/7.8; 435/7.1, 435/7.2

ABSTRACT:

Provided is a method of identifying agonists and antagonists of nuclear receptors that comprises measuring agonist-dependent fluorescence resonance energy transfer (FRET) between a fluorescently labeled nuclear receptor or ligand binding domain and fluorescently labeled CREB-binding protein (CBP), p300, other nuclear co-activator, or binding portion thereof. The method is simple, rapid, and inexpensive. Nuclear receptors and nuclear receptor co-activators labeled with fluorescent reagents for use in the above-described method are also provided.

23 Claims, 12 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 11

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 6. Document ID: US 6683080 B2

L1: Entry 6 of 25 File: USPT Jan 27, 2004

US-PAT-NO: 6683080
DOCUMENT-IDENTIFIER: US 6683080 B2

TITLE: Treatment of diabetes mellitus

DATE-ISSUED: January 27, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fryburg; David A.	East Lyme	CT		
Gibbs; Earl M.	Oakdale	CT		
Koppiker; Nandan P.	Sandwich			GB

US-CL-CURRENT: 514/242; 514/243, 514/246, 514/866

ABSTRACT:

Use of vardenafil or a pharmaceutical composition thereof in the preparation of a medicament for the curative, palliative or prophylactic treatment of type 2 diabetes mellitus.

4 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 7. Document ID: US 6667299 B1

L1: Entry 7 of 25 File: USPT Dec 23, 2003

US-PAT-NO: 6667299
DOCUMENT-IDENTIFIER: US 6667299 B1

TITLE: Pharmaceutical compositions and treatment methods

DATE-ISSUED: December 23, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ahlem; Clarence Nathaniel	San Diego	CA		
de Carvalho; Luis Daniel dos Anjos	Paio Pires			PT
Heggie; William	Palmela			PT

US-CL-CURRENT: 514/178; 552/536

ABSTRACT:

The invention provides compositions comprising, 16.alpha.-bromo-3.beta.-hydroxy-5.alpha.-androstan-17-one hemihydrate and one or more excipients, typically wherein the composition comprises less than about 3% water. The compositions are useful to make improved pharmaceutical formulations. The invention also provides methods of intermittent dosing of steroid compounds such as analogs of 16.alpha.-bromo-3.beta.-hydroxy-5.alpha.-androstan-17-one and compositions useful in such dosing regimens. The invention further provides compositions and methods to inhibit pathogen (viral) replication, ameliorate symptoms associated with immune dysregulation and to modulate immune responses in a subject using certain steroids and steroid analogs. The invention also provides methods to make and use these immunomodulatory compositions and formulations.

39 Claims, 6 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 6

☐ 8. Document ID: US 6620838 B1

L1: Entry 8 of 25 File: USPT Sep 16, 2003

US-PAT-NO: 6620838
DOCUMENT-IDENTIFIER: US 6620838 B1

TITLE: Benzopyrazone compounds, compositions thereof, and methods of treatment therewith

DATE-ISSUED: September 16, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
McKie; Jeffrey A.	San Diego	CA		
Bhagwat; Shripad S.	San Diego	CA		
Renaud; Johanne	Basil			CH
Missbach; Martin	Basil			CH

US-CL-CURRENT: 514/422; 548/525

ABSTRACT:

Benzopyranone compounds having the following structure: ##STR1##

wherein R.sub.1, X, Y and n are as defined here, are disclosed. The compounds of formula (I), wherein R.sub.1 is H, can be prepared by demethylation of the corresponding phenolic methyl ether. The compounds are useful for treating a bone-resorbing disease, cancer, arthritis or an estrogen-related condition such as breast cancer, osteoporosis and endometriosis.

33 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 9. Document ID: US 6616869 B2

L1: Entry 9 of 25 File: USPT Sep 9, 2003

US-PAT-NO: 6616869
DOCUMENT-IDENTIFIER: US 6616869 B2

TITLE: Process for preparing microparticles through phase inversion phenomena

DATE-ISSUED: September 9, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mathiowitz; Edith	Brookline	MA		
Chickering, III; Donald	Pfulgerville	TX		
Jong; Yong S.	Warwick	RI		
Jacob; Jules S.	Taunton	MA		

US-CL-CURRENT: 264/4; 264/4.1, 427/213.36

ABSTRACT:

A process for preparing nanoparticles and microparticles is provided. The process involves forming a mixture of a polymer and a solvent, wherein the solvent is present in a continuous phase and introducing the mixture into an effective amount of a nonsolvent to cause the spontaneous formation of microparticles.

37 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 10. Document ID: US 6545049 B1

L1: Entry 10 of 25 File: USPT Apr 8, 2003

US-PAT-NO: 6545049
DOCUMENT-IDENTIFIER: US 6545049 B1

TITLE: Dimer-selective RXR modulators and methods for their use

DATE-ISSUED: April 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Canan-Koch; Stacie	San Diego	CA		
Hwang; Chan K.	Boulder	CO		
Boehm; Marcus F.	San Diego	CA		
Badea; Beth Ann	San Diego	CA		
Dardashti; Laura J.	Santa Anna	CA		
Zhang; Lin	San Diego	CA		
Nadzan; Alex M.	San Diego	CA		
Heyman; Richard A.	Encinitas	CA		
Mukherjee; Ranjan	San Diego	CA		
Lala; Deepak S.	San Diego	CA		
Farmer; Luc J.	La Jolla	CA		

US-CL-CURRENT: 514/569; 514/725, 560/58

ABSTRACT:

Dimer-selective RXR modulator compounds having agonist, partial agonist and/or antagonist activity in the context of an RXR homodimer and/or RXR heterodimers are provided. Also provided are pharmaceutical compositions incorporating such dimer-selective RXR modulator compounds and methods for their therapeutic use.

36 Claims, 6 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 11. Document ID: US 6511986 B2

L1: Entry 11 of 25 File: USPT Jan 28, 2003

US-PAT-NO: 6511986
DOCUMENT-IDENTIFIER: US 6511986 B2

TITLE: Method of treating estrogen receptor positive carcinoma

DATE-ISSUED: January 28, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zhang; Yixian	Nanuet	NY		

Sadler; Tammy M.	Chester	NY
Frost; Philip	Morris Township	NJ
Greenberger; Lee Martin	Montclair	NJ

US-CL-CURRENT: 514/280; 514/183, 514/217.08, 514/291, 514/330, 514/331, 514/874, 514/922

ABSTRACT:

This invention provides a method of treating or inhibiting an estrogen receptor positive carcinoma in a mammal in need thereof, which comprises providing said mammal with an effective amount of a combination of a rapamycin and an antiestrogen.

16 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 12. Document ID: US 6489163 B1

L1: Entry 12 of 25 File: USPT Dec 3, 2002

US-PAT-NO: 6489163
DOCUMENT-IDENTIFIER: US 6489163 B1

TITLE: Ribozyme mediated inactivation of the androgen receptor

DATE-ISSUED: December 3, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Roy; Arun K	San Antonio	TX		
Chen; Shuo	San Antonio	TX		

US-CL-CURRENT: 435/375; 435/320.1, 435/325, 435/6, 435/91.31, 536/23.1, 536/23.2, 536/24.5

ABSTRACT:

The present invention provides synthetic ribozyme oligonucleotides alone and within constructs. The ribozyme gene provides methods for the treatment of prostate hyperplasia and other androgen dependent pathologies. Improved therapies for such diseases are provided without significant hormonal imbalance and without surgical intervention. Also provided are techniques for selecting and synthesizing effective and specifically targeted molecular tools for use in inhibiting androgen receptor gene expression.

21 Claims, 16 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 16

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 13. Document ID: US 6410245 B1

L1: Entry 13 of 25 File: USPT Jun 25, 2002

US-PAT-NO: 6410245
DOCUMENT-IDENTIFIER: US 6410245 B1

TITLE: Compositions and methods for detecting ligand-dependent nuclear receptor and coactivator interactions

DATE-ISSUED: June 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Northrop; Jeffrey P.	Redwood City	CA		
Hart; Charles P.	Mountain View	CA		
Schatz; Peter J.	Mountain View	CA		

US-CL-CURRENT: 435/7.1; 424/141.1, 435/69.1, 435/7.2, 436/518, 536/23.1, 536/23.5

ABSTRACT:

The invention provides methods for identifying agents that are ligands for nuclear receptors. The methods include conducting multiplexed assays utilizing positive hybrid systems, reverse hybrid systems, direct interaction assays and other assays to screen for ligands having activity with a receptor of interest. The methods can be performed in various multiplexing formats to produce a profile that can be used to categorize a test ligand relative to known agonists and antagonists.

17 Claims, 20 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 20

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 14. Document ID: US 6372739 B1

L1: Entry 14 of 25 File: USPT Apr 16, 2002

US-PAT-NO: 6372739
DOCUMENT-IDENTIFIER: US 6372739 B1

TITLE: Compounds and methods for modulation of estrogen receptors

DATE-ISSUED: April 16, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Stein; Bernd M.	San Diego	CA
Anderson; David Wesley	Poway	CA
Gayo-Fung; Leah M.	San Diego	CA
Doubleday; Mary	Doylestown	PA
Shevlin; Graziella I.	San Diego	CA
Kois; Adam	San Diego	CA
Khammungkhune; Sak	San Diego	CA
Jalluri; Ravi Kumar	San Diego	CA
Bhagwat; Shripad S.	San Diego	CA
McKie; Jeffrey A.	San Diego	CA

US-CL-CURRENT: 514/233.5; 544/151, 546/187, 546/193, 546/196, 548/311.4, 548/525, 549/289

ABSTRACT:

Compounds that modulate gene expression through the estrogen receptor (ER) are disclosed having the following structure, as well as pharmaceutical compositions containing the same: ##STR1##

wherein R.sub.1, R.sub.2, R.sub.3, n and p are as defined here. Methods are also disclosed for modulating ER in cells and/or tissues expressing the same, such as bone, breast, prostate, uterus, CNS or the cardiovascular system. Methods for treating estrogen-related conditions are also disclosed, including conditions such as is breast cancer, osteoporosis, endometriosis, cardiovascular disease, hypercholesterolemia, prostatic hypertrophy, prostatic carcinomas, obesity, hot flashes, skin effects, mood swings, memory loss, and adverse reproductive effects associated with exposure to environmental chemicals or natural hormonal imbalances.

20 Claims, 5 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

☐ 15. Document ID: US 6331562 B1

L1: Entry 15 of 25 File: USPT Dec 18, 2001

US-PAT-NO: 6331562
DOCUMENT-IDENTIFIER: US 6331562 B1
**** See image for Certificate of Correction ****

TITLE: Compounds and methods for modulation of estrogen receptors

DATE-ISSUED: December 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bhagwat; Shripad S.	San Diego	CA		
McKie; Jeffrey A.	San Diego	CA		

Khammungkhune; Sak San Diego CA

US-CL-CURRENT: 514/457; 514/456, 546/196, 548/525, 549/289

ABSTRACT:

Compounds that modulate gene expression through the estrogen receptor (ER) are disclosed having the following structure, as well as pharmaceutical compositions containing the same: ##STR1##

wherein R.sub.1, R.sub.2, R.sub.3, n and p are as defined here. In a specific embodiment, the compounds are selective modulators for Er-.beta. over ER-.alpha.. Methods are also disclosed for modulating ER-.beta. in cells and/or tissues expressing the same, including cells and/or tissues that preferentially express ER-.beta.. More generally, methods for treating estrogen-related conditions are also disclosed, including conditions such as is breast cancer, testicular cancer, osteoporosis, endometriosis, cardiovascular disease, hypercholesterolemia, prostatic hypertrophy, prostatic carcinomas, obesity, hot flashes, skin effects, mood swings, memory loss, urinary incontinence, hairloss, cataracts, natural hormonal imbalances, and adverse reproductive effects associated with exposure to environmental chemicals.

63 Claims, 5 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

☐ 16. Document ID: US 6291456 B1

L1: Entry 16 of 25 File: USPT Sep 18, 2001

US-PAT-NO: 6291456
DOCUMENT-IDENTIFIER: US 6291456 B1
**** See image for Certificate of Correction ****

TITLE: Compounds and methods for modulation of estrogen receptors

DATE-ISSUED: September 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stein; Bernd M.	San Diego	CA		
Anderson; David Wesley	Poway	CA		
Gayo-Fung; Leah M.	San Diego	CA		
Sutherland; May S.	Bothell	WA		
Doubleday; Mary	Doylestown	PA		
Shevlin; Graziella I.	San Diego	CA		
Kois; Adam	San Diego	CA		
Khammungkhune; Sak	San Diego	CA		
Jalluri; Ravi Kumar	San Diego	CA		
Bhagwat; Shripad S.	San Diego	CA		

McKie; Jeffrey A. San Diego CA

US-CL-CURRENT: 514/233.5; 544/151, 546/187, 546/193, 546/196, 548/311.4, 548/525, 549/289

ABSTRACT:

Compounds that modulate gene expression through the estrogen receptor (ER) are disclosed having the following structure, as well as pharmaceutical compositions containing the same: ##STR1##

wherein R.sub.1, R.sub.2, R.sub.3, n and p are as defined here. Methods are also disclosed for modulating ER in cells and/or tissues expressing the same, such as bone, breast, prostate, uterus, CNS or the cardiovascular system. Methods for treating estrogen-related conditions are also disclosed, including conditions such as is breast cancer, osteoporosis, endometriosis, cardiovascular disease, hypercholesterolemia, prostatic hypertrophy, prostatic carcinomas, obesity, hot flashes, skin effects, mood swings, memory loss, and adverse reproductive effects associated with exposure to environmental chemicals or natural hormonal imbalances.

78 Claims, 5 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

☐ 17. Document ID: US 6235224 B1

L1: Entry 17 of 25 File: USPT May 22, 2001

US-PAT-NO: 6235224
DOCUMENT-IDENTIFIER: US 6235224 B1
**** See image for Certificate of Correction ****

TITLE: Process for preparing microparticles through phase inversion phenomena

DATE-ISSUED: May 22, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mathiowitz; Edith	Brookline	MA		
Chickering, III; Donald	Pfulgerville	TX		
Jong; Yong S.	Warwick	RI		
Jacob; Jules S.	Taunton	MA		

US-CL-CURRENT: 264/4; 264/4.1, 427/213.36

ABSTRACT:

A process for preparing nanoparticles and microparticles is provided. The process involves forming a mixture of a polymer and a solvent, wherein the solvent is present in a continuous phase and introducing the mixture into an effective amount of a nonsolvent to cause the spontaneous formation of microparticles.

4 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

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☐ 18. Document ID: US 6218128 B1

L1: Entry 18 of 25 File: USPT Apr 17, 2001

US-PAT-NO: 6218128
DOCUMENT-IDENTIFIER: US 6218128 B1
**** See image for Certificate of Correction ****

TITLE: Methods of identifying compounds having nuclear receptor negative hormone and/or antagonist activities

DATE-ISSUED: April 17, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliott S.	Marina Del Rey	CA		
Nagpal; Sunil	Lake Forest	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 435/7.1

ABSTRACT:

Methods of characterizing and identifying negative hormones of nuclear receptors. Also disclosed are methods of making modulators of retinoid nuclear receptor transactivation activity, assays for agonists, antagonists, and negative hormones of the RAR receptor, and specific retinoid modulators of retinoid nuclear receptors.

21 Claims, 30 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 20

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

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☐ 19. Document ID: US 6143211 A

L1: Entry 19 of 25 File: USPT Nov 7, 2000

US-PAT-NO: 6143211
DOCUMENT-IDENTIFIER: US 6143211 A
**** See image for Certificate of Correction ****

TITLE: Process for preparing microparticles through phase inversion phenomena

DATE-ISSUED: November 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mathiowitz; Edith	Brookline	MA		
Chickering, III; Donald	Pfulgerville	TX		
Jong; Yong S.	Warwick	RI		
Jacob; Jules S.	Taunton	MA		

US-CL-CURRENT: 264/4; 264/4.1, 427/213.36

ABSTRACT:

A process for preparing nanoparticles and microparticles is provided. The process involves forming a mixture of a polymer and a solvent, wherein the solvent is present in a continuous phase and introducing the mixture into an effective amount of a nonsolvent to cause the spontaneous formation of microparticles.

31 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 20. Document ID: WO 3083488 A2

L1: Entry 20 of 25 File: EPAB Oct 9, 2003

PUB-NO: WO003083488A2
DOCUMENT-IDENTIFIER: WO 3083488 A2
TITLE: METHOD FOR IDENTIFYING STAT AFFECTING AGENTS

PUBN-DATE: October 9, 2003

INVENTOR-INFORMATION:

NAME	COUNTRY
BJORNSTROM, LINDA	SE
SJOBERG, MARIA	SE

INT-CL (IPC): G01 N 33/74; G01 N 33/50; C07 K 14/47; C12 N 5/00
EUR-CL (EPC): G01N033/50; G01N033/74

ABSTRACT:

CHG DATE=20040128 STATUS=O>The present invention relates to a method for identifying an agonist and an antagonist of a cytoplasmic estrogen receptor (ER). The present invention also relates to determining if an agent affects the ability of a cytoplasmic agonist-bound estrogen receptor (ER) to mediate phosphorylation of one or more Signal Transducer and Activator of Transcription (STAT) proteins. The present invention also relates to the use of a cytoplasmic ER agonist, antagonist or an agent that affects the ability of a cytoplasmic agonist-bound ER to mediate phosphorylation of one or more STAT proteins, in the treatment of prophylaxis of a disease caused by abnormal phosphorylation of one of more STAT proteins. For

example, the disease may be a cardiovascular disease, osteoporosis, an immune disease, a psychological disease such as memory loss or depression, oncogenesis, tumour progression, inflammation or diabetes.

Terms	Documents
estrogen receptor same (agonist or diethylstilbestrol or DES) same (activator or coactivator)	25

Hit List

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 21 through 25 of 25 returned.

☐ 21. Document ID: WO 9907847 A1

Using default format because multiple data bases are involved.

L1: Entry 21 of 25 File: EPAB Feb 18, 1999

PUB-NO: WO009907847A1
DOCUMENT-IDENTIFIER: WO 9907847 A1
TITLE: HUMAN ESTROGEN RECEPTOR-BETA

PUBN-DATE: February 18, 1999

INVENTOR-INFORMATION:

NAME	COUNTRY
BHAT, RAMESH A	
HENDERSON, RUTH ANN	
HSIAO, CHULAI	
KARATHANASIS, SOTIRIOS KONSTANT	

INT-CL (IPC): C12 N 15/12; C07 K 14/705; C07 K 16/28; G01 N 33/68
EUR-CL (EPC): C07K014/705

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 22. Document ID: WO 2004052286 A2

L1: Entry 22 of 25 File: DWPI Jun 24, 2004

DERWENT-ACC-NO: 2004-487807
DERWENT-WEEK: 200446

TITLE: New pyrazolo pyrimidine derivatives are tyrosine kinase inhibitors useful to treat or prevent e.g. cancers, diabetic retinopathy, age-related macular degeneration, macular edema, retinal ischemia and inflammatory diseases

INVENTOR: FRALEY, M E; HAMBAUGH, S R ; HUNGATE, R W ; RUBINO, R S

PRIORITY-DATA: 2002US-432453P (December 11, 2002)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 2004052286 A2	June 24, 2004	E	087	A61K000/00

INT-CL (IPC): A61 K 0/00

ABSTRACTED-PUB-NO: WO2004052286A
BASIC-ABSTRACT:

NOVELTY - Pyrazolo pyrimidine derivatives (I) and their salts, stereoisomers are new.

DETAILED DESCRIPTION - Pyrazolo pyrimidine derivatives of formula (I) and their salts, stereoisomers are new.

A = aryl or heterocyclyl;

R1 = T' or N(R5)2;

T' = 1-10C alkyl, 3-6C cycloalkyl, 2-10C alkenyl, 2-10C alkynyl, aryl, heterocyclyl, O-1-6C alkyl-NR5R6, NO2, OR6 (where the alkyl, cycloalkyl, alkenyl, alkynyl, aryl or heterocyclyl is optionally substituted (os) by one or more R7);

R1a = 1-10C alkyl, 3-6C cycloalkyl, aryl, heterocyclyl (all os) or H;

R2, R3 = L';

L' = 1-6C alkyl (os), 1-3C perfluoroalkyl, H, OR6 or halo;

R4a = NR5(CR1a2)nR8, NR5(CR1a2)nOR5, R8S(O)mR8, NR5(CR1a2)nC(O)NR5R6, halo, 2-6C alkenyl(CR1a2)nOR5, 2-6C alkynyl(CR1a2)nOR5, OR5, C(O)R5, R8, NR5(CR1a2)nNR5R6, R8C(O)NR5(CR1a)nNR5R6, C(O)NR5(CR1a2)nR8, C(O)OR5, C(O)NR5(CR1a2)nNR5R6 or C(O)NR5(CR1a2)nOR5;

R4b = T' or NR5R6;

R5, R6 = H, halo, aralkyl, (CO)Ob1-10C alkyl, (CO)Ob3-8C cycloalkyl, (CO)Obaryl, (CO)Obheterocyclyl, 1-10C alkyl, aryl, 2-10C alkenyl, 2-10C alkynyl, heterocyclyl, 3-8C cycloalkyl, SO2Ra or (CO)NRb2 (where the alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, alkenyl or alkynyl is os with one or more R7a) or R5 + R6 and the nitrogen atom to which they are attached together form a monocyclic or bicyclic heterocycle with 5-7 members in ring optionally containing in addition to the N, 1-2 additional heteroatoms of N, O or S (where the monocyclic or bicyclic heterocycle os with R7);

R7 = (C=O)aOb1-10C alkyl, (CO)aOb aryl, 2-10C alkenyl, 2-10C alkynyl, (CO)aOb heterocyclyl, CO2Ra, halo, CN, ORa, Ob1-6C perfluoroalkyl, Oa(CO)bNR5R6, oxo, C(O)Ra, (NO)R5R6 or (CO)aOb3-8C cycloalkyl (where the alkyl, aryl, alkenyl, alkynyl, heterocyclyl or cycloalkyl os with one or more R7a);

R7a = (CO)aOb1-10C alkyl, Oa(1-3C perfluoroalkyl), (0-6C alkyl)-S(O)mRa, oxo, ORa, halo, CN, 2-10C alkenyl, 2-10C alkynyl, 3-6C cycloalkyl, (0-6C alkyl)-aryl, (0-6C alkyl)-heterocyclyl, (0-6C alkyl)-N(Rb)2, C(O)Ra or (0-6C alkyl)-CO2H (where the alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclyl is os with up to 3 Rb, OH, 1-6C alkoxy, halo, CO2H, CN, O(CO)1-6C alkyl, oxo, N(Rb)2 or N(Rb)-(1-6C alkyl)-N(Rb)2);

R8 = 1-10C alkyl, aryl, heterocycle or 3-10C (all os by one or more R7);

Ra = K';

Rb = K', aralkyl, (C=O)O1-6C alkyl, (C=O)1-6C alkyl or S(O)2Ra;

K' = H, 1-6C alkyl, 3-6C cycloalkyl, aryl or heterocyclyl;

a, b = 0-1;

m, s = 0-2;

n, p = 0-6; and

t = 0-3.

INDEPENDENT CLAIMS are also included for

(1) a pharmaceutical composition comprising (I) and a pharmaceutically acceptable carrier; and

(2) (I) can be used in combination with radiation therapy, radiation therapy, an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an 3-hydroxy-3-methyl glutaryl COA (HMG-CoA) reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, peroxisome proliferator activator receptor (PPAR) - gamma agonists, PPAR- delta agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, agent useful in the treatment of neutropenia, and an immunologic-enhancing drug, paclitaxel or trastuzumab and GPIIb/IIIa antagonist to treat cancer.

ACTIVITY - Cytostatic; Antiangiogenic; Ophthalmological; Vasotropic; Antidiabetic; Antiinflammatory; Antiarthritic; Antirheumatic; Antipsoriatic; Dermatological; Antiallergic; Immunosuppressive; Cerebroprotective; Osteopathic.

MECHANISM OF ACTION - Tyrosine kinase inhibitor.

USE - (I) are used to treat or prevent cancers (such as cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung, histiocytic lymphoma, lung adenocarcinoma, small cell lung cancers, pancreatic cancer, gioblastomas and breast carcinoma), a disease in which angiogenesis is implicated (preferably ocular disease), retinal vascularization, diabetic retinopathy, age-related macular degeneration, macular edema, retinal ischemia, inflammatory diseases (such as rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions), tyrosine kinase-dependent diseases or conditions, tissue damage following a cerebral ischemic event and bone associated pathologies (such as osteosarcoma, osteoarthritis and rickets) (claimed).

(I) were tested for their vascular endothelial growth factor (VEGF)-stimulated mitogenesis inhibitory activity in human vascular endothelial cells using human umbilical vein endothelial cell mitogenesis assay. The median inhibitory concentration of (I) was found to be 0.001-5 mu M.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 23. Document ID: AU 2003263402 A1, WO 2004026823 A1, US 20040110767 A1

L1: Entry 23 of 25 File: DWPI Apr 8, 2004

DERWENT-ACC-NO: 2004-295354
DERWENT-WEEK: 200462

TITLE: New amide and sulfonamide compounds are estrogen receptor ligands used for treating e.g. female sexual dysfunction, postmenopausal syndrome, osteoporosis, elevated serum cholesterol levels and breast and uterine cancer

INVENTOR: CAMERON, K O; CHESWORTH, R

PRIORITY-DATA: 2002US-412338P (September 20, 2002), 2003US-0666811 (September 17, 2003)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 2003263402 A1	April 8, 2004		000	C07D207/06
WO 2004026823 A1	April 1, 2004	E	143	C07D207/06
US 20040110767 A1	June 10, 2004		000	A61K031/4965

INT-CL (IPC): A61 K 31/40; A61 K 31/4025; A61 K 31/445; A61 K 31/4965; A61 K 31/505; C07 D 207/06; C07 D 207/08; C07 D 207/16; C07 D 211/14; C07 D 211/44; C07 D 213/38; C07 D 213/72; C07 D 217/04; C07 D 233/61; C07 D 295/135; C07 D 307/14; C07 D 409/12; C07 D 413/12

ABSTRACTED-PUB-NO: WO2004026823A
BASIC-ABSTRACT:

NOVELTY - Amide and sulfonamide compounds (I) are new.

DETAILED DESCRIPTION - Amide and sulfonamide compounds of formula (I), their salts, stereoisomers and prodrugs are new.

Q = phenyl substituted by R9 and Z or 6-membered heteroaryl containing 1 or 2 N heteroatoms (optionally substituted by R9 and/or Z);

R1-R3, R9 = 1-6C alkyl or 1-6C alkoxy (both optionally substituted by 1-3 F), H, OH, halo or CN;

R4 = H or 1-6C alkyl;

R5 = 1-7C alkyl (optionally substituted by 1-6 halo, 2-6C alkenyl, (2-6C alkenyl)-M or (CH2)n-M;

n = 0-5;

M = fully saturated 3-8 membered ring or partially or fully saturated 5-8 membered ring optionally containing 1-4 O, N or S heteroatoms or a bicyclic ring comprising two fused 5- or 6-membered rings optionally containing 1-4 O, N or S heteroatoms (all optionally substituted by 1-3 OH, halo, CN, NO2, formyl, NH2, carbamoyl, thiol or 1-6C alkyl or 1-6C alkoxy (both optionally substituted by 1-5 halo), 3-8C cycloalkyl or phenyl (both optionally substituted by 1-3 halo), SO(1-6C alkyl) or SO2(1-6C alkyl) (both optionally substituted by 1-5 halo), S(1-6C alkyl) (optionally substituted by 1-5 halo), 1-4C alkoxycarbonyl, 1-6C alkyl-(3-6C cycloalkyl), 0-4C sulfonamido, mono-N or di-N,N-(1-4C alkylcarbamoyl), mono-N or di-N,N-(1-4C alkylamino)-SO2, mono-N or di-N,N-(1-4C alkylamino), 1-8C alkanoyl, 1-4C alkanoylamino or 1-4C alkoxycarbonylamino);

Z = O(CH2)n-NRaRb, (CH2)n-NRaRb, CH=CH-C(O)-NRaRb, (CH2)n-COOH, CH=CH-COOH, 1-6C alkoxy, CH=CH-C(O)O-(1-6C alkyl) or (CH2)n-OH;

X = CO or SO2, and

Ra, Rb = H, 1-6C alkyl, (CH2)n-3-8C cycloalkyl, (CH2)2-5-OH, (CH2)n-phenyl, (CH2)n-heteroaryl, (CH2)n-heterocycloalkyl, phenyl-CH-1-6C alkyl or phenyl-CH-phenyl (where cycloalkyl, phenyl, heteroaryl and heterocycloalkyl are optionally substituted by 1-3 OH, halo, CN, NO2, NH2, carbamoyl, or 1-6C alkyl or 1-6C alkoxy (both optionally substituted by 1-5 halo), (1-3C alkyl)-O-(1-3C alkyl), (1-4C)OH (sic), carboxylate, 1-3C phenyl (sic), 3-8C cycloalkyl, phenyl (optionally substituted by 1-3 halo), or SO(1-6C alkyl), SO2(1-6C alkyl) or S(1-6C alkyl) (all optionally substituted by 1-5 halo), 1-4C alkoxycarbonyl, (1-6C alkyl)-(3-8C cycloalkyl), sulfonamido, 1-4C alkylsulfonamido, mono-N or di-N,N-1-4C alkylcarbamoyl, mono-N or di-N,N-1-4C alkylamino-SO2, mono-N or di-N,N-1-4C alkylamino, 1-8C alkanoyl, 1-4C alkanoylamino or 1-4C alkoxycarbonylamino), or

NRaRb = 3-7 membered heterocycloalkyl containing 1 or 2 N, O or S heteroatoms or 5-7 membered ring fused to a phenyl ring (both optionally substituted by 1-3 OH, halo, CN, NO2, NH2, carbamoyl, or 1-6C alkyl or 1-6C alkoxy (both optionally substituted by 1-5 halo, (1-3C alkyl)-O-(1-3C alkyl), (1-4C)OH (sic), carboxylate, 1-3C phenyl (sic), 3-8C cycloalkyl, phenyl (optionally substituted by 1-3 halo), or SO(1-6C alkyl) SO2(1-6C alkyl) or S(1-6C alkyl) (all optionally substituted by 1-5 halo), 1-4C alkoxycarbonyl, (1-6C alkyl)-(3-8C cycloalkyl), 0-4C sulfonamido, 1-4C cycloalkylsulfonamido, mono-N or di-N,N-1-4C alkylcarbamoyl, mono-N or di-N,N-1-4C alkylamino-SO2, mono-N, or di-N,N-1-4C alkylamino, 1-8C alkanoyl, 1-4C alkanoylamino or 1-4C alkoxycarbonylamino),

provided that when Z is O-(CH2)n-NRaRb, n is 2-5.

ACTIVITY - Endocrine-Gen.; Gynecological; Osteopathic; Antilipemic; Cytostatic; Dermatological; Cardiovascular-Gen.; Neuroprotective; Nootropic; Anorectic; Gynecological; Antiseborrheic; Depilatory; Hemostatic; Antiinfertility; Antiulcer; Antiinflammatory; Vasotropic; Antiarteriosclerotic; Immunosuppressive; Cardiant; Thrombolytic; Hypotensive; Antirheumatic; Antiarthritic; Antithyroid; .

MECHANISM OF ACTION - Estrogen receptor agonist; Estrogen receptor antagonist; Calcium channel blocker; Plasminogen activator inhibitor.

Tests are described but no results given.

USE - Useful for treating female sexual dysfunction, perimenopausal or postmenopausal syndrome, osteoporosis, atrophy of skin or vagina, elevated serum cholesterol levels, cardiovascular disease, Alzheimer's disease, reduction or preventing reduction in cognitive function, estrogen dependent cancer, breast and uterine cancer, prostatic disease, prostate cancer, obesity, endometriosis, bone loss, uterine fibrosis, aortal smooth muscle cell proliferation, lack of birth control, acne, hirsutism, dysfunctional uterine bleeding, dysmenorrhea, male infertility, impotence, psychological and behavioral symptoms during menstruation, ulcerative mucositis, uterine fibroids disease, restenosis, atherosclerosis, musculaponeurotic fibromatosis, alopecia, autoimmune disease, cartilage degeneration, delayed puberty, demyelinating disease, dysmyelinating disease, hypoglycemia, lupus erythematosus, myocardial infarction, ischemia, thromboembolic disorder, obsessive compulsive disorder, ovarian dysgenesis, post menopausal central nervous system disorder, pulmonary hypertension, reperfusion damage, resistant neoplasm, rheumatoid arthritis, seborrhea, sexual precocity, thyroiditis, Turner's syndrome and hyperlipidemia, blocking calcium channels, inhibiting environmental estrogens, minimizing the uterotropic effect of tamoxifen and its analogs, removing fibrin by inhibiting plasminogen activators, inhibiting estrogen-positive primary tumors of the brain and CNS, increasing sphincter competence, increasing libido, inhibiting fertility, oxidizing low-density lipoprotein, increasing macrophage function, expressing thrombomodulin and increasing levels of endogenous growth hormone (all claimed).

☐ 24. Document ID: AU 2003226530 A1, WO 2003083488 A2

L1: Entry 24 of 25 File: DWPI Oct 13, 2003

DERWENT-ACC-NO: 2003-804102
DERWENT-WEEK: 200435

TITLE: Identifying an agonist or antagonist of a cytoplasmic estrogen receptor (ER) for treating or preventing e.g., diabetes comprises contacting a cell with a candidate agonist, or with an ER agonist and a candidate antagonist

INVENTOR: BJORNSTROM, L; SJOBERG, M

PRIORITY-DATA: 2002GB-0007738 (April 3, 2002)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 2003226530 A1	October 13, 2003		000	G01N033/74
WO 2003083488 A2	October 9, 2003	E	071	G01N033/74

INT-CL (IPC): C07 K 14/47; C12 N 5/00; G01 N 33/50; G01 N 33/74

ABSTRACTED-PUB-NO: WO2003083488A
BASIC-ABSTRACT:

NOVELTY - Identifying an (ant)agonist of a cytoplasmic estrogen receptor (ER) that leads to the phosphorylation of a Signal Transducer and Activator of Transcription (STAT) protein comprising contacting a cell comprising a STAT responsive reporter construct, a STAT protein and a cytoplasmic ER with a candidate agonist, or with an ER agonist and a candidate antagonist, is new.

DETAILED DESCRIPTION - Identifying an agonist or antagonist of a cytoplasmic estrogen receptor (ER) that leads to the phosphorylation of a Signal Transducer and Activator of Transcription (STAT) protein or that inhibits the action of a cytoplasmic ER in the presence of an agonist to mediate the phosphorylation of a STAT protein comprises contacting a cell comprising a STAT responsive reporter construct, a STAT protein and a cytoplasmic ER with a candidate agonist, or with an ER agonist and a candidate antagonist, where the cell has intact Src-kinase, MAP-kinase and P13-kinase signaling pathways.

INDEPENDENT CLAIMS are included for:

(1) identifying an agonist of a cytoplasmic estrogen receptor (ER) that leads to the phosphorylation of a Signal Transducer and Activator of Transcription (STAT) protein comprising contacting a cell comprising a STAT responsive reporter construct, a STAT protein and a cytoplasmic ER with a candidate agonist;

(2) identifying an antagonist of a cytoplasmic estrogen receptor (ER) that inhibits the action of a cytoplasmic ER in the presence of an agonist to mediate the phosphorylation of a STAT protein comprising contacting a cell comprising a STAT responsive reporter construct, a STAT protein and a cytoplasmic ER with an ER agonist and a candidate antagonist;

(3) determining if an agent affects the ability of an agonist-bound cytoplasmic ER to mediate phosphorylation of a STAT protein;

(4) an agonist of a cytoplasmic ER that leads to the phosphorylation of a STAT protein;

(5) an antagonist of a cytoplasmic ER that inhibits the action of a cytoplasmic ER in the presence of an agonist to mediate the phosphorylation of a STAT protein;

(6) an agent that affects the ability of a cytoplasmic agonist-bound ER to mediate phosphorylation of a STAT protein or that affects the ability of an agonist-bound ER to initiate transcription from an ERE receptor construct and/or affects the ability of an agonist or antagonist-bound ER to potentiate transcription from a STAT5-bound ER to mediate phosphorylation of a STAT protein;

(7) treating or preventing a disease caused by abnormal proliferation of one or more STAT proteins;

(8) an ER that has been modified so that it accumulates in the cytoplasm of a cell to a greater degree than the corresponding wild type ER; and

(9) a eukaryotic cell for use in the methods of the invention.

ACTIVITY - Cardiant; Immunomodulator; Cytostatic; Antiinflammatory; Antidiabetic.

No biological data given.

MECHANISM OF ACTION - Gene Therapy.

No biological data given.

USE - The antagonist and/or agonist of a cytoplasmic ER or a novel agent that affects the ability of a cytoplasmic ER to mediate phosphorylation of a STAT protein or a novel agent that does not affect the ability of an agonist-bound ER to mediate phosphorylation of a STAT factor but does affect the ability of a cytoplasmic agonist-bound ER to initiate transcription from an ERE reporter construct is useful in manufacturing a medicament for treating or preventing a disease caused by abnormal phosphorylation of one or more STAT proteins (all claimed), e.g., cardiovascular, immune or psychological disorder, tumor, inflammation or diabetes.

☐ 25. Document ID: WO 200210188 A1, AU 200182016 A, NO 200300419 A, EP 1307471 A1, BR 200112791 A, CZ 200300270 A3, SK 200300088 A3, KR 2003029640 A, HU 200301592 A2, CN 1444596 A, JP 2004505093 W, US 20040043976 A1, ZA 200300417 A

L1: Entry 25 of 25 File: DWPI Feb 7, 2002

DERWENT-ACC-NO: 2002-382411
DERWENT-WEEK: 200469

TITLE: New 16-alpha-methyl or ethyl substituted steroidal estrogens useful for estrogen-receptor related treatment e.g. estrogen receptor alpha selective treatment

INVENTOR: LOOZEN, H J J; MESTRES, J ; VEENEMAN, G H

PRIORITY-DATA: 2000EP-0202697 (July 28, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200210188 A1	February 7, 2002	E	024	C07J001/00
AU 200182016 A	February 13, 2002		000	C07J001/00
NO 200300419 A	January 27, 2003		000	C07J001/00
EP 1307471 A1	May 7, 2003	E	000	C07J001/00
BR 200112791 A	June 24, 2003		000	C07J001/00
CZ 200300270 A3	June 18, 2003		000	C07J001/00
SK 200300088 A3	July 1, 2003		000	C07J001/00
KR 2003029640 A	April 14, 2003		000	C07J001/00
HU 200301592 A2	September 29, 2003		000	C07J001/00
CN 1444596 A	September 24, 2003		000	C07J001/00
JP 2004505093 W	February 19, 2004		039	C07J001/00
US 20040043976 A1	March 4, 2004		000	A61K031/56
ZA 200300417 A	June 30, 2004		032	C07J000/00

INT-CL (IPC): A61 K 31/56; A61 K 31/565; A61 K 31/567; A61 K 31/569; A61 P 5/30; A61 P 15/12; A61 P 15/18; A61 P 43/00; C07 J 0/00; C07 J 1/00; C07 J 7/00; C07 J 51/00; C07 J 71/00

ABSTRACTED-PUB-NO: WO 200210188A
BASIC-ABSTRACT:

NOVELTY - 16- alpha -Methyl or ethyl substituted steroidal compounds (I) are new.

DETAILED DESCRIPTION - 16- alpha -Methyl or ethyl substituted steroidal compounds of formula (I) are new.

R1 = 1-3C alkyl or 2-3C alkenyl (both optionally substituted with halo);

R2 = 1-4C alkyl, 2-4C alkenyl or methylene (all optionally substituted with halo);

R3 = methyl or ethyl.

Ring A is fully saturated, aromatic or saturated with Delta 5-10 double bonds.

ACTIVITY - Osteopathic; Cytostatic; Cardiant; Gynecological; Antidepressant; Nootropic; Neuroprotective.

MECHANISM OF ACTION - alpha -Estrogen receptor activator or agonist.

Test details are described but no biological data is given.

USE - (I) Are used in the manufacture of a medicament for an estrogen-receptor related treatment such as estrogen receptor alpha selective treatment, hormone replacement therapy or contraception (all claimed). The estrogen-receptor related disorders are pre- and/or post-menopausal complaints and osteoporosis.

(I) are also useful in treating or preventing benign prostate hypertrophy, cardiovascular disorders, estrogen dependent tumor control or central nervous system disorders such as depression or Alzheimer's disease.

ADVANTAGE - The compound is selective for the estrogen receptor of the alpha - subtype.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Terms	Documents
estrogen receptor same (agonist or diethylstilbestrol or DES) same (activator or coactivator)	25

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Previous Page Next Page Go to Doc#